Remarks

New claim 109 is added herein. Support for new claim 109 can be found throughout the specification, such as on page 3, line 1; page 16, line 24, page 10, line 29; page 14 line 8 and page 25, line 6. Claim 59 and 60-65 are amended herein. Support for the amendment of claim 59 can found throughout the specification, such as on page 7, lines 10-15 and Fig. 5. Claims 60-65 are amended to correct form.

Claims 67, 78, 86, 103-108 are amended herein to depend from claim 59. Claims 67-68, 71-78, 80-86, 88-90, 92-102 and 108 were withdrawn from consideration as being drawn to a non-elected invention.

Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks.

Rejections under 35 U.S.C. § 102

Claims 59-65 and 103-107 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Gronthos et al., (*J. of Dental Research* 81(8): 531-535, 2002). Applicants respectfully disagree with this rejection.

As noted in the Office action, Gronthos et al. discloses dental pulp stem cells (DPSCs) obtained from amputated human third molars of adults (19-29 years old; see page 531) and compares these cells to human bone marrow stromal stem cells (BMSSCs, also known as BMSCs). The Office alleges that although the cells disclosed in Gronthos et al. are isolated from adults, DPSCs are identical to the dental pulp stem cells isolated from deciduous teeth claimed in the current application.

DPSCs are multipotent and capable of differentiating into adipocytes and neural cells (see page 534). In addition, these cells can differentiate into adipocytes and neuronal cells (see page 534, and the abstract). Gronthos et al. state that "DPSCs do not grow extensively *ex vivo*" and describes that the celsl are heterogenous in their ability to proliferate (see page 534). Specifically, Gronthos et al. state that DPSCs "contain sub-populations of cells with different proliferative rates and different differentiation potentials, a property similar to BMSSCs" (see page 534, second column). Gronthos et al. disclose that the majority of DPSCs "proliferated for

less than 20 population doublings" (see page 534 and FIG. 4A). The remaining DPSCs proliferate for 20 to 30 population doublings (see page 535). Gronthos et al. disclose that only 67% of the DPSCs were able to form abundant amounts of dentin.

The specification provides ample evidence that human postnatal deciduous dental pulp multipotent stem cells from exfoliated teeth (*i.e.*, stem cells from a human exfoliated deciduous tooth or "SHED"; see page 10, lines 17-20 of the specification) are not the same as DPSCs, such as those cells disclosed by Gronthos et al. For example, the specification teaches that "when compared to ... dental pulp stem cells (DPSCs), SHED showed a higher proliferation rate (Figure 5G) and a higher number of population doublings (Figure 5H)" (see page 25, lines 3-5 and Figures 5G and 5H of the specification). In fact, as shown in Figure 5H, SHED can proliferate to over 140 population doublings. This evidence alone demonstrates the claimed human postnatal deciduous dental pulp multipotent stem cells are novel over the DPSCs disclosed by Gronthos et al.

Furthermore, the claimed cells are not obvious in view of Gronthos et al. It would not be obvious to one of skill in the art to isolate stem cells from exfoliated deciduous teeth because of the extensive differences between exfoliated deciduous teeth and amputated permanent teeth. In particular, the anatomical changes to a deciduous tooth that occur before exfoliation render such exfoliated deciduous teeth dramatically different from amputated adult teeth. For example, the roots of deciduous teeth completely resorb prior to exfoliation and replacement by a permanent tooth (see page 634 of Sahara *et al.*, J. Dent. Res., 72:634-640, 1993, copy attached as Exhibit A). Hard (calcified) surfaces are resorbed via acid and protease release by the surrounding tissues followed by the resorption of the inner part of the root (see pages 308-309 of Oshiro *et al.*, The Anatomical Record, 264:305-311, 2001, copy attached as Exhibit B). Concurrent to resorption, an epithelial cell layer forms over the nascent permanent tooth and the coronal base of the (soon to be exfoliated) deciduous tooth (Sahara *et al.*, page 634). Further, any soft tissue (*e.g.*, dental pulp) remaining within an exfoliated deciduous tooth exhibits dense inflammatory infiltration (Sahara *et al.*, page 634). With the resorption of the root and formation of this epithelial cell layer, blood supply to any remaining dental pulp within the deciduous tooth is severely disrupted (Sahara *et al.*, page 640), so very little bleeding is observed upon shedding of a deciduous tooth. (Sahara *et al.*, page 640). Considering the anatomical changes, dense inflammatory infiltration and the disrupted blood supply known to be present in exfoliated

deciduous teeth, it is completely unexpected that exfoliated deciduous teeth would contain any type of functional cell, much less a multipotent stem cell with a very high ability to proliferate. Instead, one of skill in the art would expect that the tissues of exfoliated deciduous teeth would be dead or dying and, absent evidence to the contrary, would not expect such discarded tissues to contain stem cells, let alone stem cells that can proliferate for an increased number of population doublings.

Thus, the claimed cells are clearly both novel and non-obvious in view of the cells disclosed by Gronthos et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 59-65 and 103-107 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Gronthos et al., (*PNAS* 97(25): 13625-13630, 2000). Applicants respectfully disagree with this rejection.

Gronthos et al. discloses dental pulp stem cells (DPSCs) obtained from amputated human third molars of adults (19-29 years old; see page 13625) and compares these cells to human bone marrow stromal cells (BMSCs). The Office alleges that although the cells disclosed in Gronthos et al. are isolated from adults, the cells are identical to the dental pulp stem cells isolated from deciduous teeth claimed in the current application. Applicants respectfully disagree.

The Office action acknowledges that he cells disclosed by Gronthos et al. are multipotent cells isolated from a different source, namely from molars collected from adults aged 19-29 years. The Office action asserts that since the disclosed cells are stem cells isolated from teeth, they must inherently be the same as the claimed cells. The Office action asserts that the burden is on the Applicants to show that there is an unobvious difference between the cells disclosed by Gronthos and the claimed cells.

The Applicants submit that they have met this burden, and have clearly demonstrated that the claimed cells are different from the DPSCs disclosed by Gronthos et al. As discussed above, the specification provides ample evidence that claimed cells, termed human postnatal deciduous dental pulp multipotent stem cells from exfoliated teeth (*i.e.*, stem cells from a human exfoliated deciduous tooth or "SHED"; see page 10, lines 17-20 of the specification) are not the same as DPSCs. As discussed above, the specification teaches that "when compared to ... dental pulp stem cells (DPSCs), SHED showed a higher proliferation rate (Figure 5G) and a higher number

of population doublings (Figure 5H)" (see page 25, lines 3-5 and Figures 5G and 5H of the specification). As shown in Fig. 5G, the claimed cells proliferate at a much higher rate that the DPSCs described by Gronthos et al. Specifically, the claimed cells incorporate bromodeoxyuridine (BrdU) at a much higher rate than the cells disclosed by Gronthos et al. (see Figure 5G), and proliferate to over 140 population doublings, while the DPSCs disclosed by Gronthos et al. proliferate to only 100 population doublings. This evidence alone renders the human postnatal deciduous dental pulp multipotent stem cells of the invention novel over the DPSCs disclosed by Gronthos et al. Solely to advance prosecution, the claims have been amended to recite that the claimed cells can proliferate to over 140 population doublings.

Additionally, Gronthos et al. teaches that DPSCs lack capacity to form adipocytes (see Gronthos et al., page 13625, abstract). However, the claimed human postnatal deciduous dental pulp multipotent stem cells from exfoliated teeth do form adipocytes (see page 26, lines 3-9 and Figure 10 of the specification). Thus, the presently claimed cells have unique characteristics that are very different from the cells disclosed by Gronthos et al.

Furthermore, the claimed cells are not obvious in view of Gronthos et al. As discussed above, it would not be obvious to one of skill in the art to isolate stem cells from exfoliated deciduous teeth because of the extensive differences between exfoliated deciduous teeth and amputated permanent teeth. In particular, the anatomical changes to a deciduous tooth that occur before exfoliation render such exfoliated deciduous teeth dramatically different from amputated adult teeth (see 634 of Sahara *et al.*, J. Dent. Res., 72:634-640, 1993 and pages 308-309 of Oshiro *et al.*, The Anatomical Record, 264:305-311, 2001, both of which are discussed in more detail above). Considering the anatomical changes, dense inflammatory infiltration and the disrupted blood supply known to be present in exfoliated deciduous teeth, it is completely unexpected that exfoliated deciduous teeth would contain any type of functional cell, much less a multipotent stem cell. Thus, one of skill in the art would predict that the tissues of exfoliated deciduous teeth would be dead or dying and, absent evidence to the contrary, would not expect such discarded tissues to contain stem cells, let alone stem cells that can proliferate for a large number of population doublings.

Thus, the claimed cells are clearly novel and non-obvious in view of the cells disclosed by Gronthos et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 59-65 and 103-107 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Shi et al., (PCT Publication No. WO 02/07679, January 2002). Applicants respectfully disagree with this rejection.

Shi et al. discloses dental pulp stem cells (DPSCs) obtained from amputated human third molars of adults of at least 18 years of age (see page 6), such as subjects 19-29 years of age (see page 9). Shi et al. compares these cells to human bone marrow stromal stem cells (BMSCs, see page 13). Shi et al. disclose that the DPSCs can form dentin-like structures *in vivo*. In addition, Shi et al. disclose that DPSCs proliferate twice as much as BMSSCs. The Office alleges that although the cells disclosed in Shi et al. are isolated from adults, DPSCs are identical to the dental pulp stem cells isolated from deciduous teeth claimed in the current application.

As discussed above, DPSCs are very different than the claimed cells. The specification provides evidence that human postnatal deciduous dental pulp multipotent stem cells from exfoliated teeth (*i.e.*, stem cells from a human exfoliated deciduous tooth or "SHED"; see page 10, lines 17-20 of the specification) are not the same as DPSCs, such as those disclosed by Shi et al. For example, the specification teaches that the proliferation rate of the claimed cells is different than DPSCs, such as those described in Shi et al. (see Figures 5G and 5H of the specification, which are discussed in more detail above). As disclosed in the specification, the claimed cells (SHED) can proliferate to over 140 population doublings, while DPSCs only proliferate for up to 100 population doublings. Thus, SHED have at least a 150% higher proliferative capacity when compared to DPSCs. This evidence alone renders the claimed human postnatal deciduous dental pulp multipotent stem cells novel over the DPSCs disclosed by Shi et al.

Furthermore, the claimed cells are not obvious in view of Shi et al., for the reasons discussed above. Specifically, it would not be obvious to one of skill in the art to isolate stem cells from exfoliated deciduous teeth because of the extensive differences between exfoliated deciduous teeth and amputated permanent teeth. In particular, the anatomical changes to a deciduous tooth that occur before exfoliation render such exfoliated deciduous teeth dramatically different from amputated adult teeth (see Sahara *et al.*, J. Dent. Res., 72:634-640, 1993; Oshiro *et al.*, The Anatomical Record, 264:305-311, 2001, both discussed in detail above). It would be completely unexpected to one of skill in the art that exfoliated deciduous teeth would contain any type of functional cell, much less a multipotent stem cell with a high potential to proliferate.

Specifically, one of skill in the art would expect that the tissues of exfoliated deciduous teeth would be dead or dying. Absent any evidence to the contrary, one of skill in the art would not expect discarded tissues to contain stem cells, let alone stem cells that can proliferate for an increased number of population doublings when compared to stem cells isolated from living molars (such as those from adult subjects of at least 18 years of age).

Thus, the claimed cells are clearly novel and non-obvious in view of the cells disclosed by Shi et al. Reconsideration and withdrawal of the rejection are respectfully requested

Claims 59-65 and 103-107 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Shi et al., (*Bone* 29(6): 532-539, 2001) as evidenced by Gronthos et al., (*PNAS* 97(25): 13625-13630, 2000) and Gronthos et al., (*J. of Dental Research* 81(8): 531-535, August 2002).

As discussed above, DPSCs are very different than the claimed cells. Furthermore, the specification provides ample evidence that human postnatal deciduous dental pulp multipotent stem cells from exfoliated teeth (*i.e.*, stem cells from a human exfoliated deciduous tooth or "SHED"; see page 10, lines 17-20 of the specification) are not the same as DPSCs, such as those disclosed by Shi et al. For example, the specification teaches that dental pulp stem cells (DPSCs) have a lower proliferation rate, which the claimed cells (SHED) have a much higher proliferation rate (Figure 5G) and a higher number of population doublings (Figure 5H)" (see page 25, lines 3-5 and Figures 5G and 5H of the specification). As shown in Figure 5H, SHED can proliferate to over 140 population doublings, while DPSCs only proliferate for up to 100 population doublings. Thus, SHED have at least a 150% higher proliferative capacity as compared to DPSCs. This evidence alone renders the claimed human postnatal deciduous dental pulp multipotent stem cells novel over the DPSCs disclosed by Shi et al.

Furthermore, the claimed cells are not obvious in view of Shi et al. As discussed above, it would not be obvious to one of skill in the art to isolate stem cells from exfoliated deciduous teeth because of the extensive differences between exfoliated deciduous teeth and amputated permanent teeth. For the reasons set forth above, it would be completely unexpected to one of skill in the art that exfoliated deciduous teeth would contain any type of functional cell, much less a multipotent stem cell with a high potential to proliferate.

Thus, the claimed cells are also clearly novel and non-obvious in view of the cells disclosed by Shi et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection under 35 U.S.C. § 103

Claim 65 was rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Gronthos et al., (*PNAS*, 97(25): 13625-13630, 2000) and Nakashima et al., (*Gene Therapy* 9(12): 814-818, June 2002).

Gronthos et al. is discussed above. Gronthos et al. disclose human DPSCs obtained from adult teeth, which are very different than the presently claimed cells. Furthermore, there is nothing in Gronthos et al. that suggests, nor renders obvious the isolation of stem cells from deciduous teeth, nor is there anything in Gronthos et al. that can be construed to teach or suggest that stem cells isolated from human deciduous teeth would have specific characteristics, such as the ability to differentiate into a neural cell, an adipocyte, or an odontoblast; the expression of CD146; and/or that the cells could proliferate for over 140 population doublings.

Nakashima et al. teaches electroporation-mediated delivery of growth/differentiation factor 11 (Gdf11) cDNA into the amputated pulp of canine teeth of adult dogs (page 816-817 and Figure 5 of Nakashima et al.). Nakashima et al. disclose that the transfer of Gdf11 gene into dental pulp cells from adult dogs induced the formation of new reparative dentin.

However, Nakashima et al. does not make up for the deficiencies of Gronthos et al. There is nothing in Nakashima et al. that suggest isolating stem cells from human deciduous teeth. Furthermore, there is no teaching in Nakashima et al. that could be construed to teach the characteristics of the claimed cells, such as that they differentiate into a neural cell, an adipocyte, or an odontoblast; express CD146, or proliferate for over 140 population doublings.

Thus, Nakashima et al. does not make up for the deficiencies of Gronthos et al. Reconsideration and withdrawal of the rejection is respectfully requested.

Request for Rejoinder

The examiner has required restriction between product and process claims. As set forth in MPEP § 821.04, when applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise

require all the limitations of the allowable product claim should be considered for rejoinder. It is the Applicants understanding that all claims directed to a nonelected process that include all the limitations of an allowable product claim will be rejoined. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR §1.104. The method claims are amended herein to ensure they are dependent on claim 59, or a dependent claim thereof, to ensure they are in condition for rejoinder.

Conclusion

The present response adequately addresses all of the rejections asserted in the Office action. If anything further is required prior to the issuance of a Notice of Allowance, or the examination of the method claims, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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